4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2023-N-0062]

Medical Devices; Hematology and Pathology Devices; Classification of the Software Algorithm Device to Assist Users in Digital Pathology

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is classifying the software algorithm device to assist users in digital pathology into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for the software algorithm device to assist users in digital pathology's classification. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on September 21, 2021.

FOR FURTHER INFORMATION CONTACT: Arpita Roy, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3319, Silver Spring, MD, 20993-0002, 240-402-4807, Arpita.Roy@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the software algorithm device to assist users in digital pathology as class II (special controls), which we have determined will provide a reasonable

assurance of safety and effectiveness. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (see 21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act. Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) modified the De Novo application process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 510(k) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under

section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining "substantial equivalence"). Instead, sponsors can use the less-burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On December 31, 2020, FDA received Paige.AI, Inc.'s request for De Novo classification of the Paige Prostate. FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see 21 U.S.C. 360c(a)(1)(B)). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has

determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on September 21, 2021, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 864.3750.[1] We have named the generic type of device software algorithm device to assist users in digital pathology, and it is identified as an in vitro diagnostic device intended to evaluate acquired scanned pathology whole slide images. The device uses software algorithms to provide information to the user about presence, location, and characteristics of areas of the image with clinical implications. Information from this device is intended to assist the user in determining a pathology diagnosis.

FDA has identified the following risks to health associated specifically with this type of device and the measures required to mitigate these risks in table 1.

Table 1.--Software Algorithm Device To Assist Users in Digital Pathology Risks and Mitigation Measures

Identified Risks	Mitigation Measures
False negative classification (loss of accuracy)	Certain design verification and validation, including certain device descriptions, certain analytical studies, and clinical studies; and Certain labeling information, including certain device descriptions, certain performance information, and certain limitations.
False positive classification (loss of accuracy)	Certain design verification and validation, including certain device descriptions, certain analytical studies, and clinical studies; and Certain labeling information, including certain device descriptions, certain performance information, and certain limitations.

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this order. This device is subject to premarket notification requirements under section 510(k) of the FD&C Act.

[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

III. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 860, subpart D, regarding De Novo classification have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions, have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820, regarding quality system regulation, have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR parts 801and 809, regarding labeling, have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 864

Blood, Medical devices, and Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 864 is amended as follows:

PART 864--HEMATOLOGY AND PATHOLOGY DEVICES

1. The authority citation for part 864 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Add § 864.3750 to subpart D to read as follows:

§ 864.3750 Software algorithm device to assist users in digital pathology.

(a) *Identification*. A software algorithm device to assist users in digital pathology is an in vitro diagnostic device intended to evaluate acquired scanned pathology whole slide images. The device uses software algorithms to provide information to the user about presence, location, and characteristics of areas of the image with clinical implications. Information from this device is intended to assist the user in determining a pathology diagnosis.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) The intended use on the device's label and labeling required under § 809.10 of this chapter must include:

(i) Specimen type;

(ii) Information on the device input(s) (e.g., scanned whole slide images (WSI), etc.);

(iii) Information on the device output(s) (e.g., format of the information provided by the device to the user that can be used to evaluate the WSI, etc.);

(iv) Intended users;

(v) Necessary input/output devices (e.g., WSI scanners, viewing software, etc.);

(vi) A limiting statement that addresses use of the device as an adjunct; and

(vii) A limiting statement that users should use the device in conjunction with complete standard of care evaluation of the WSI.

(2) The labeling required under § 809.10(b) of this chapter must include:

(i) A detailed description of the device, including the following:

(A) Detailed descriptions of the software device, including the detection/analysis algorithm, software design architecture, interaction with input/output devices, and necessary third-party software;

(B) Detailed descriptions of the intended user(s) and recommended training for safe use of the device; and

(C) Clear instructions about how to resolve device-related issues (e.g., cybersecurity or device malfunction issues).

(ii) A detailed summary of the performance testing, including test methods, dataset characteristics, results, and a summary of sub-analyses on case distributions stratified by relevant confounders, such as anatomical characteristics, patient demographics, medical history, user experience, and scanning equipment, as applicable.

(iii) Limiting statements that indicate:

(A) A description of situations in which the device may fail or may not operate at its expected performance level (e.g., poor image quality or for certain subpopulations), including any limitations in the dataset used to train, test, and tune the algorithm during device development;

(B) The data acquired using the device should only be interpreted by the types of users indicated in the intended use statement; and

(C) Qualified users should employ appropriate procedures and safeguards (e.g., quality control measures, etc.) to assure the validity of the interpretation of images obtained using this device.

(3) Design verification and validation must include:

(i) A detailed description of the device software, including its algorithm and its development, that includes a description of any datasets used to train, tune, or test the software algorithm. This detailed description of the device software must include:

(A) A detailed description of the technical performance assessment study protocols (e.g., regions of interest (ROI) localization study) and results used to assess the device output(s) (e.g., image overlays, image heatmaps, etc.);

(B) The training dataset must include cases representing different pre-analytical variables representative of the conditions likely to be encountered when used as intended (e.g., fixation type and time, histology slide processing techniques, challenging diagnostic cases, multiple sites, patient demographics, etc.);

(C) The number of WSI in an independent validation dataset must be appropriate to demonstrate device accuracy in detecting and localizing ROIs on scanned WSI, and must include subsets clinically relevant to the intended use of the device;

(D) Emergency recovery/backup functions, which must be included in the device design;

(E) System level architecture diagram with a matrix to depict the communication endpoints, communication protocols, and security protections for the device and its supportive systems, including any products or services that are included in the communication pathway; and

(F) A risk management plan, including a justification of how the cybersecurity vulnerabilities of third-party software and services are reduced by the device's risk management mitigations in order to address cybersecurity risks associated with key device functionality (such as loss of image, altered metadata, corrupted image data, degraded image quality, etc.). The risk management plan must also include how the device will be maintained on its intended platform (e.g. a general purpose computing platform, virtual machine, middleware, cloud-based computing services, medical device hardware, etc.), which includes how the software integrity will be maintained, how the software will be authenticated on the platform, how any reliance on the platform will be managed in order to facilitate implementation of cybersecurity controls (such as user authentication, communication encryption and authentication, etc.), and how the device will be protected when the underlying platform is not updated, such that the specific risks of the device are addressed (such as loss of image, altered metadata, corrupted image data, degraded image quality, etc.).

(ii) Data demonstrating acceptable, as determined by FDA, analytical device performance, by conducting analytical studies. For each analytical study, relevant details must be documented (e.g., the origin of the study slides and images, reader/annotator qualifications, method of annotation, location of the study site(s), challenging diagnoses, etc.). The analytical studies must include:

(A) Bench testing or technical testing to assess device output, such as localization of ROIs within a pre-specified threshold. Samples must be representative of the entire spectrum of challenging cases likely to be encountered when the device is used as intended; and

(B) Data from a precision study that demonstrates device performance when used with multiple input devices (e.g., WSI scanners) to assess total variability across operators, within-scanner, between-scanner and between-site, using clinical specimens with defined, clinically relevant, and challenging characteristics likely to be encountered when the device is used as intended. Samples must be representative of the entire spectrum of challenging cases likely to be encountered when the device is used as intended. Precision, including performance of the device and reproducibility, must be assessed by agreement between replicates.

(iii) Data demonstrating acceptable, as determined by FDA, clinical validation must be demonstrated by conducting studies with clinical specimens. For each clinical study, relevant details must be documented (e.g., the origin of the study slides and images, reader/annotator qualifications, method of annotation, location of the study site(s) (on-site/remote), challenging diagnoses, etc.). The studies must include:

(A) A study demonstrating the performance by the intended users with and without the software device (e.g., unassisted and device-assisted reading of scanned WSI of pathology slides). The study dataset must contain sufficient numbers of cases from relevant cohorts that are representative of the scope of patients likely to be encountered given the intended use of the device (e.g., subsets defined by clinically relevant confounders, challenging diagnoses, subsets with potential biopsy appearance modifiers, concomitant diseases, and subsets defined by image scanning characteristics, etc.) such that the performance estimates and confidence intervals for these individual subsets can be characterized. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., sensitivity, specificity, predictive value, diagnostic likelihood ratio, etc.).

(B) [Reserved]

Dated: January 26, 2023.

Lauren K. Roth,

Associate Commissioner for Policy

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